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09/374,554	08/13/1999	ANDREW W. SHYJAN	MRI-005CP2	3905

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EXAMINER

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ART UNIT

PAPER NUMBER

1634

11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/374,554	SHYLAN ET AL.
	Examiner	Art Unit
	Jeanine A Goldberg	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- THE MAILING DATE OF THIS COMMUNICATION IS 01/10/2023.

 - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
 - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 November 2001 .

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-40 is/are pending in the application.

4a) Of the above claim(s) 1,2,4,5,7-11,13,14,16,17,19,20,22-26,28,29,31,34 and 37-40 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 3,6,12,15,18,21,27,30,32,33,35 and 36 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. ____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III in Paper No. 9 is acknowledged. Prior to allowance, non-elected subject matter will be required to be cancelled.
2. Claim 40 has been removed, as approved by DeAnn Smith, from each of the groups and placed in its own group because it is a distinct method which requires additional method steps and considerations which was inadvertently included with each of the groups.
3. Applicant's have elected BST2 as the single sequence. The examiner notes that this appears to receive benefit of the August 13, 1999 date of the instantly filed case.
4. Claims 3, 6, 12, 15, 18, 21, 27, 30, 32, 33, 35, 36 have been examined to the extend that the read upon the elected sequence, namely BST-2.

Drawings

5. The drawings are objected to because the tables are not clear with respect to which numbers are designed to be directed to which table headings. Moreover, the text appears to have been copied numerous times blurring some of the letters, words and numbers.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. The specification is objected to because on page 45, the specification contains a blank which is not filled in. Applicant is reminded that no new matter may be entered.

Priority

8. This application claims priority to 09/322,864 and 09/233,611 in addition to three provisional applications.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). It is noted that the application contains a reference to the prior applications, however this references does not conform to the guidelines set forth in the MPEP 201. For example, the references does not indicate whether the applications are continuations, divisions, or continuations in part. Appropriate correction is required.

Sequence Rules

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

For example on page 36 and 46, the specification describes a primer, but fails to provide any SEQ ID NO: for the sequence. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3, 6, 12, 15, 18, 21, 27, 30, 32, 33, 35, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

Breadth of the Claims

The claims are broadly drawn to methods of determining whether TAXOL cannot be used to reduce the growth of cancer cells, and methods for determining whether or not treatment with TAXOL should be continued in a cancer patient by determining the expression level of BST2.

Guidance and Direction Presented and Working Examples

The specification teaches cancer cell lines are used to determine whether genes and/or ESTs are sensitive or resistant (page 34). These nucleic acids were places upon

an Affymetrix GeneChip systems and analyzed with respect to the hybridization patterns and intensities. This appears as though it was used to identify which nucleic acids are expressed in cancer cell lines and what how they were affected by different agents. Example 2, page 40, teaches identification of sensitivity and resistance genes *in vivo*. Each of these studies relates to cisplatin and cyclophosphamide. The specification states, page 41, that "the gene descriptions refer to sequence immobilized on an Affymetrix HUM6000 gene chip and that the names associated with the sequences may not be the actual names of the genes that are hybridizing to the bound probe." On page 44, Example 5, the specification teaches three studies which are directed to TAXOL. Genes are identified which are relatively highly expressed in TAXOL resistant cell lines. The levels of expression in mammary epithelial cell primary cell lines and breast cancer cell lines were compared. Moreover, breast cancer clinical samples which appeared to respond well and poorly to TAXOL were compared.

The state of the Art

BST-2 expression

The art teaches that BST-2 is expressed in human cell lines including those with the origin of hepatoma, bladder cell carcinoma, glioblastoma and cervical cancer carcinoma (Ishikawa et al. Genomics, Vol. 26, pages 527-534, 1995). Ishikawa also illustrates that BST-2 mRNA are expressed in a variety of tissues including pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart.

Taxol Screening Methods

The art teaches characterization of taxol-induced apoptosis and altered gene expression in human breast cancer cells (Cheng et al. Cellular Pharmacology, Vol 2,

pages 249-257, 1995). Cheng teaches using a PCR-mediated differential screening procedure and Northern analysis, 12 taxol response genes were identified from human breast tumour cell line that are either up- or down-regulated by taxol (abstract, Table 1).

Taxol sensitivity not related to p53 expression levels

Borbe et al (Cancer Chemother Pharmacol. Vol 44, pages 217-227, 1999) teaches an analysis of a panel of 12 human glioma cell lines which revealed no relationship between genetic or functional p53 status and taxol sensitivity. Moreover, Borbe teaches "activity of taxol against malignant glioma cell lines in vitro has been shown in several studies. However, despite the remarkable in vitro potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity" (page 218, col. 1).

As provided in the art, p53 is commonly overexpressed in gliomas. Pykett et al (International J. of Oncology, Vol. 13, No. 2, pages 213-216, August 1998-abstract only) teaches that gliomas are part of a subset of tumors in which overexpression of p53 protein in the absence of p53 gene mutation has been described.

Cell lines not indicative of Tumors

Dermer et al. (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer et al. state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

Orr et al. (J. of the National Cancer Institute, Vol 92, No. 12, June 21, 2000, pages 987-994) teaches that the normal cells were used to avoid the genetic complexities associated with established cell lines. Orr suggests that cellular studies using normal human cells in which the complexity of the system can be carefully controlled by the addition of one, two or even more genes associated with cancer development may provide valuable information about how the products of the genes interact with each other and which combinations are critical in regulating chemosensitivity.

Eastham et al. (Int. J. Radiat. Biol. Vol. 77, No. 3, pages 295-302, 2001) teaches that "poor correlation between the different endpoints precludes their use in a clinical setting on primary tumour samples in vitro. It may be that tumour cell lines in vitro are a poor model for tumours in vivo. Studies aimed at assessing assays for measuring tumour radiosensitivity therefore should employ clinical samples. In vitro cell line work should concentrate on unraveling the complex mechanisms involved in determining a radiosensitive or radioresistant phenotype" (page 295, col 1, abstract). Moreover, Eastham teaches that "using cell lines derived from a single tumour type no correlation was found between clonogenic survival and the two different endpoints studied" (page 299, col 2).

Undue experimentation and unpredictability of the art

As a preliminary matter, the specification is confusing as to whether breast cancer patients or ovarian cancer patients were studied on page 50. On page 45, the

specification appears to be describing a study which samples breast cancer clinical samples obtained from patients whose breast cancer appeared to respond toTAXOL/cisplatin combination therapy and breast cancer clinical samples which appeared to respond poorly (lines 17-25). The specification further states that the genes which were identified are provided in Table 11A and 11B. However, on page 50, the specification discusses differential expression of genes in responsive and non-responsive ovarian cancer. The specification discusses ovarian cancer patients who responded both well and poorly were sampled and the results of the genes identified are in Table 11A and 11B (lines 10-20). This appears to be conflicting to the statements on page 46. However, the specification also teaches that the clinical samples were patients undergoing breast cancer therapy (lines 22-24). Therefore, it is unclear what data is provided in Table 11A and 11B.

The problem with the claims, particularly Claim 3 and narrower Claim 18 is the absence of correlation between the resistance gene chosen and any evidence that the gene has a relationship to TAXOL resistance itself. For example, a gene determined as expressed in TAXOL resistance cells may be a gene expressed by all cells. BST-2 appears to be such a gene. As provided in Ishikawa, BST-2 is expressed in pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart tissues as well as hepatoma, bladder cell carcinoma, glioblastoma, and cervical cell carcinoma cell lines. So absence of a correlation of BST2 or any of the genes in the Tables provided renders Claim 18 non-enabled because the gene is not evidenced to be a resistance gene. Its differential expression upon exposure to TAXOL may be indicative of apoptosis, for

example, and not TAXOL resistance. Over expression alone is not proof of taxol resistance. Under such a notion, Figure 7 of Ishikawa would illustrate, that heart muscle which appear to express BST-2 at higher levels than the kidney would imply that kidney tissue would be TAXOL sensitive whereas heart tissue would be resistant to TAXOL because BST-2 is over expressed. The specification teaches that for BST-2 three of the four cell lines studied for sensitivity illustrated that expression of BST-2 was present, albeit at lower levels than the two resistant cell lines.

Neither the specification nor the art teaches how to make and use the invention as broadly as claimed. First, cancer cell lines are not indicative of patient samples. The elected BST2 gene appears in Table 9B. Table 9B appears to be a list of genes that are relatively highly expressed in selected relatively TAXOL resistant breast cancer cell lines compared to selected relatively TAXOL sensitive breast cancer cell lines (page 47, lines 33-37). As noted above, the specification does not appear to have studied patient samples from breast cancer individuals. Cancer cell lines have been taught in the art not to be appropriate models for patient samples. The specification fails to provide any evidence that a similar pattern of TAXOL resistance is present in actual tumor tissue from a clinical patient. The expression pattern of BST-2 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this mRNA would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue. Borbe teaches, "activity of taxol against malignant glioma cell lines in vitro has been shown in several studies. However, despite the remarkable in vitro potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas

showed no relevant activity" (page 218, col. 1). Borbe thus stands for the proposition that genes, namely p53, shown to be over expressed in glioma cell lines are not associated, and further they are not associated *in vivo*. Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Furthermore, Orr teaches that the normal cells were used to avoid the genetic complexities associated with established cell lines. While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use BST-2 as a method for cancer diagnosis and/or detection with any reliability. As discussed by Dermer *et al.*, Orr *et al* and Eastham, the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention would require unreasonable experimentation on the part of the practitioner to further screen actual tumor tissue to test for a connection between BST-2 expression and cancer resistance to TAXOL. In light of the teachings in the prior art, and the general unpredictability concerning the activity of BST-2 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Even in the event that the Table 11A was directed to genes which are relatively expressed at a relatively high level in TAXOL/cisplatin resistant clinical samples from breast cancer patients as compared to TAXOL/cisplatin sensitive clinical samples, the study includes an additional agent, namely cisplatin, and also does not contain the BST-2 gene. Therefore, there is no indication that patient cells treated with TAXOL alone would be indicative of the inability for TAXOL to be used to reduce the growth of cells. The combination of the two drugs may have varying effects on the gene expression such that different results are obtained between samples treated with TAXOL alone and with TAXOL in combination with cisplatin. Furthermore, BST2 does not appear to be among those genes which are identified to be relatively highly expressed in the clinical trials. Therefore, this appears to support the notion that there is no noticeable correlation between cell lines and patient samples. In the event that cell lines and patient samples were similar, the genes which are expressed at a relatively higher level in cell lines should be very similar to those genes identified to be expressed at a relatively higher level in patient samples.

Secondly, different cancers act in different manners. The specification appears to clearly illustrate that different genes are expressed in relatively higher manners for different cancer cell lines. For example, the specification sample colon, breast, ovarian, and melanoma. The genes which appear to be relatively highly expressed in relatively TAXOL resistant cell lines appear to differ between the different cell lines, indicating that not all genes are differentially expressed in different cancer cell lines. For example, determination that BST-2 is relatively highly expressed in breast cancer cell lines does

not provide any indication of how this gene functions in any other type of cancer cell lines. The different variety of cancers affect different genes such that the expression of one gene is not indicative of how the gene would act in a different cancer type.

Thirdly, the specification appears to only sample TAXOL resistant cell lines, however does not appear subjecting any cancer cells to TAXOL and assaying for BST2 mRNA expression. Since the mechanisms of TAXOL and how the agent works within cells is unknown, merely using cell lines which are "TAXOL resistant" does not appear to simulate subjecting cells to the TAXOL agent. The TAXOL resistant cells have not been subjected to an agent, namely TAXOL, they are only believed to have some resistance to TAXOL. The studies which involved clinical samples had been subjected to the TAXOL agent and had been subjected to the agent in vivo. There is no indication how cells treated with TAXOL which keep growing respond to expression levels of BST2. The specification teaches sampling cells and assaying for expression of mRNA in vitro. The specification has not provided any teachings with respect to sampling the expression of mRNA in vivo. There is no indication that TAXOL is what causes the different expression patterns of the genes when only TAXOL resistant cells are studied. The specification additionally does not appear to consider that TAXOL affects a gene which is involved in a pathway or cascade which is either upstream or downstream of BST2. Therefore, the apparent relatively high expression of the gene in a TAXOL resistant cell line does not appear to provide correlation to clinical sample which have actually been treated with TAXOL. As stated above, these studies appear to yield

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different results, therefore, the determination of an in vivo study does not appear to correlate with in vitro studies.

Finally, as clearly admitted and pointed out in the specification, page 41, "the gene descriptions refer to sequence immobilized on an Affymetrix HUM6000 gene chip and that the names associated with the sequences may not be the actual names of the genes that are hybridizing to the bound probe." Therefore, the specification appears to indicated that the identification of the actual names of the genes may not be truly what was identified. Therefore, without assaying for the true known gene BST2 it is unpredictable that the sequences hybridizing to the bound probe are in fact the nucleic acid sequences of BST2.

Therefore, in order to practice the claimed invention as a whole as broadly as claimed, the skilled artisan would be required to perform extensive additionally experimentation with unpredictable results. The skilled artisan would be required to determine how the gene functions in an environment which is different than the cell lines which were studied in the specification. The skilled artisan would be required to determine how the gene functions with respect to the specific cancer of interest of the patient. Finally, the skilled artisan would be required to determine how the application of TAXOL in vitro differs, if it does, to the application of TAXOL in vivo.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 3, 6, 12, 15, 18, 21, 27, 30, 32, 33, 35, 36, and 40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 3, 6, 12, 15 is indefinite. Claims 3, 6, 12, 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: directed to how to determine whether TAXOL cannot be used to reduce the growth by merely obtaining cells, determining expression of genes in those cells. It appears as though the claim is missing a step directed to treating with TAXOL. Without a step directed to treatment with TAXOL, the claim would not use TAXOL to reduce the growth of cancer cells in any situation where genes are expressed.

B) Claim 15 is indefinite because it is unclear how the Claim further limits Claim 3 to which it depends. Claim 3 has been amended to recite TAXOL, rather than an agent. Additionally, the claim lacks antecedent basis for "said agent".

C) Claims 18, 21, 27, 30 are indefinite. Claims 18, 21, 27, 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are directed to a step which provides a threshold or comparison to determine what increased. The final process step provides that the expression of one or more genes is increased in the presence of TAXOL, but it does not provide how the determination of increased expression is made. Without a comparison to a sample

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which was not treated with the TAXOL or another such comparison, the method appears to be missing steps and/or elements.

D) Claim 30 is indefinite because it is unclear how the Claim further limits Claim 18 to which it depends. Claim 18 has been amended to recite TAXOL, rather than an agent. Additionally, the claim lacks antecedent basis for "said agent".

E) 32-33, 35-36 are indefinite because it is unclear whether the two samples are taken simultaneously such that the samples represent the same time in the treatment process or whether one sample is taken at time point number one and the second sample is taken three weeks later, for example, at time point two and a comparison is made to determine how the expression is changing over time. In the event that applicant's intend the former, it is unclear how an increase during the course of treatment would be assessed. There does not appear to be any comparison or threshold to base expression level upon. Thus, the metes and bounds of the claimed invention are unclear.

Conclusion

12. No claims allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday- Friday 7:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
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February 8, 2002

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